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Association of the Blood/Air Partition Coefficient of 1,3-Butadiene with Blood Lipids and Albumin

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Pulmonary gas uptake is a function of the blood solubility of a vapor, indicated by the blood/air partition coefficient. We hypothesized that blood lipid compositions are associated with the blood/air partition coefficients of lipophilic toxic vapors such as 1,3-butadiene. Our goal was to investigate cross-sectional and longitudinal relationships of blood triglycerides, total cholesterol, and albumin to the blood/air partition coefficient of butadiene. We collected blood samples from 24 subjects at three time points: a fasting baseline and 2 and 4 hr after drinking a standardized high-fat milk shake (107 g fat, 80 g sugar, and 27 g protein). The blood/air partition coefficient was determined using the closed vial-equilibrium technique. Triglycerides and total cholesterol were analyzed by an enzymatic method, and albumin was analyzed with an immunoassay technique. We used multiple linear regression and general linear models to examine the cross-sectional and longitudinal relationship, respectively. The results showed that the blood/air partition coefficient of butadiene was cross-sectionally associated only with triglycerides at baseline, and longitudinally related to baseline triglycerides, total cholesterol, and the change in triglycerides over time. The blood/air partition coefficient of butadiene increased, on average, by approximately 20% and up to 40% for subjects with borderline higher triglyceride levels after ingestion of a standardized milk shake. In addition, a time factor beyond lipids was also significant in predicting the blood/air partition coefficient of butadiene. This may represent the effects of other unmeasured parameters related to time or time of day on the blood/air partition coefficient of butadiene. Because the blood/air partition coefficient is a major determinant of gas uptake, ingestion of a high fat meal before this type of exposure may significantly increase an individual's absorbed dose, possibly increasing the risk of adverse effects. **Key words:** albumin, blood/air partition coefficient, total cholesterol, triglycerides. *Environ Health Perspect* 110:165–168 (2002). [Online 16 January 2002]

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The solubility of a volatile chemical in blood, indicated as the blood/air partition coefficient, has been shown to be one of the most important physicochemical properties in determining the respiratory kinetics of volatile chemicals or vapors in humans (1,2). The blood/air partition coefficient is calculated as the equilibrium ratio of the blood to air concentrations at body temperature. Traditionally, the average for a group rather than individual values has been used in either estimating the risk from exposure to air pollutants or calculating administered anesthetics dose (3,4). However, using the group average value would be inappropriate if there was large variation in the blood/air partition coefficients, across people, or even within the same individual across time, because this might lead to a poor estimate of the amount of absorbed vapor in individuals (5). Thus it is critical to characterize variation in the blood/air partition coefficients of chemicals to examine the effects of toxic gases and vapors.

The blood/air partition coefficients of several lipophilic chemicals such as 1,1,1-trichloroethane have been found to be associated with blood constituents such as total cholesterol and triglycerides (6).

1,3-Butadiene (BD; C₄H₆; CAS No. 106-99-0) is a lipophilic chemical (logarithm of the *n*-octanol/water partition coefficient of BD is 1.99) (7) that is commonly used as a raw material in the petrochemical industry. It is a major feed stock in the production of butyl rubber and acrylonitrile-butadiene-styrene (ABS) plastic. BD is also a common contaminant found in urban air pollution from combustion emissions, gasoline vapor, and cigarette smoking (8). It has been reported that increasing exposure to BD is associated with excess mortality from lymphohematopoietic cancers in both humans and animals (9). Therefore, it is important to understand the factors that determine the blood/air partition coefficient of BD, which is crucial for the inhalation kinetics of BD (10).

The objective of the present study was to examine the relationship of the blood/air partition coefficient of BD to blood lipids, specifically triglycerides and total cholesterol, and albumin. First, we examined the cross-sectional association of the blood/air partition coefficient of BD with blood triglycerides, total cholesterol, and albumin at baseline after overnight fasting. To have a better understanding of the association of interest, we also explored the longitudinal relationship of the

blood/air partition coefficient of BD to blood constituents by studying the changes in the blood parameters of interest over time after ingestion of a standardized high-fat milk shake. The effect of unmeasured parameters on variation in the blood/air partition coefficient across individuals could be minimized using each subject as his/her own control in a repeated measurements design.

Methods and Materials

Study design. After overnight fasting, a baseline venous blood sample was collected. The subject then ingested a standardized high-fat milk shake, which was followed by the collection of two additional blood samples at 2 and 4 hr after ingesting the milk shake. Each blood sample (20 mL) was divided into three parts to determine the blood/air partition coefficient for BD, plasma lipids, and serum albumin. The milk shake contained 12 oz ice cream, 180 mL whole milk, and 120 mL heavy cream, which had 107 g fat (69 g saturated fatty acid), 80 g carbohydrate (sugar), and 27 g protein. During the 4-hr study period, the subject abstained from food or anything to drink except water. A questionnaire was administered to collect demographic and lifestyle information including smoking and alcohol consumption. Both smoking and alcohol consumption were recorded based upon current status (Yes/No).

Study subjects. The Human Subjects Committee of the Harvard School of Public Health approved the human study protocol. Participation by human subjects did not occur until after informed consent was obtained. Volunteers were informed of the potential hazards of repeated blood draws. The protocol did not involve exposing the subjects to BD. Determination of the blood/air partition coefficient is a separate laboratory procedure. Exposure of laboratory

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personnel was also minimized. A total of 24 healthy participants were recruited to this study from the Boston, Massachusetts, area. Volunteers who were taking oral contraceptives, using lipid-lowering medications, or who had metabolic or cardiovascular diseases were excluded from this study.

Determination of the blood/air partition coefficient, blood lipids, and albumin. To determine the blood/air partition coefficient of BD, we used a modification of the closed-vial, headspace equilibration approach (11,12) and the National Institute for Occupational Safety and Health analytical method for the measurement of BD (13). Briefly, for the headspace method, we used a gas-tight syringe (Hamilton Company, Reno, NV) to spike 50 μ L pure BD vapor (> 99.99%) (Aldrich Chemical Co., Milwaukee, WI) into a closed 20 mL vial containing a 6 mL blood sample. The vial was placed in a 37°C oven for 2 hr until reaching equilibrium (14), and then duplicate 1-mL gas samples were taken from the headspace of the vial and analyzed with gas chromatography to determine the mass of BD in the gas phase. We calculated the amount of BD in the blood phase as the difference between the initially added BD and the

recovered BD in the gas phase after correcting for recovery losses. The blood/air partition coefficient was then calculated as the ratio of the concentration of BD between headspace air and blood.

Plasma was immediately separated from the blood samples and stored at -80°C for analyses of triglycerides and total cholesterol using an enzymatic method (Boehringer-Mannheim, Mannheim, Germany) (15) in Frank M. Sacks's laboratory at the Harvard School of Public Health. Six hours after blood samples were collected, serum albumin was analyzed at the Brigham and Women's Hospital (Boston, MA) using a selective multiprotein analyzer Behring Nephelometer (Dade Behring Inc., Newark, DE) and the modified immunoassay polychromatic technique (16).

Statistical analysis. The cross-sectional relationship of blood/air partition coefficient of BD to blood triglycerides, total cholesterol, and albumin was examined using Spearman correlation coefficients and multiple regression analyses. In addition, we used *t*-tests, analysis of variance (ANOVA), or nonparametric Wilcoxon rank-sum tests (if the distributions were skewed) to compare the blood/air partition coefficient of BD

with respect to sex, alcohol consumption, and cigarette smoking. We also assessed potential confounding factors and interaction terms when building the final cross-sectional regression model. Transformations were performed as needed to normalize the dependent variables before regression analyses. Linearity assumptions were examined using residual plots.

In the longitudinal analyses, paired-sample *t*-tests or nonparametric Wilcoxon signed-rank tests for skewed distributions were used to examine whether triglycerides, total cholesterol, or albumin significantly changed over time. To differentiate the cross-sectional from longitudinal effects, we regressed the repeated observations on the blood/air partition coefficient of BD on baseline triglycerides, total cholesterol, albumin, and changes in these blood parameters using the general linear models (17). We used unrestricted covariance structures with restricted maximum likelihood (REML) and empirical (robust) estimation of standard errors to estimate the regression parameters across the population of 24 subjects (18). Confounding factors, interaction term, and other covariates were also examined based upon biological plausibility. We used SAS PROC GLM for cross-sectional analyses and PROC MIXED for longitudinal analyses (19). The level of significance of all analyses was set at 0.05.

Results

Baseline blood constituents and postprandial changes. The 24 eligible participants consisted of 15 males and 9 females at 32 \pm 10 years of age (mean \pm SD; range 23–56 years) and with a body mass index (BMI) of 26 \pm 4 kg/m² (range 20–37 kg/m²). Five subjects were current smokers at the time of recruitment, and 13 of these participants had at least one alcoholic drink every week. The self-reported racial distribution was 12 whites, 6 Hispanics, 5 Asians, and 1 African American. Table 1 shows baseline blood/air partition coefficients of BD and blood parameters, along with the change in blood parameters following ingestion of the milk shake. The blood/air partition coefficient of BD increased significantly by 0.31 \pm 0.17 (mean \pm SD) at 4 hr after drinking the milk shake (p < 0.001), which was an approximate 20%

Table 1. Fasting baseline blood constituents and postprandial changes (n = 24 subjects).

	Fasting baseline	Change ^a	
		Baseline to 2 hr	Baseline to 4 hr
Blood/air partition coefficient of BD	1.57 \pm 0.14 (1.22–1.84)	0.19 \pm 0.09* (0.05–0.41)	0.31 \pm 0.17* (0.07–0.78)
Triglycerides, mmol/L	1.40 \pm 0.84 (0.61–3.78)	1.21 \pm 0.66* (0.17–2.93)	1.72 \pm 1.23* (0.29–5.21)
Total cholesterol, mmol/L	5.01 \pm 0.99 (3.43–8.46)	0.17 \pm 0.71 (-1.29–1.79)	0.00 \pm 0.58 (-1.29–1.38)
Albumin, g/dL	4.79 \pm 0.28 (4.30–5.30)	0.03 \pm 0.18 (-0.30–0.40)	0.01 \pm 0.20 (-0.30–0.40)

Values shown are mean \pm SD (range).

^aChange from the baseline level. Comparisons were made using pair-sample *t*-tests; the Wilcoxon signed-rank test was used to examine the change in triglycerides over 4 hr (baseline to 4 hr) due to skewness in the variable. *Significant change from baseline (p \geq 0.05).

Table 2. Spearman correlation coefficients (cross-sectional associations) between fasting baseline blood/air partition coefficient of BD, blood lipid, albumin, age, and BMI (n = 24 subjects).

	Blood/air partition coefficient of BD	Triglyceride	Total cholesterol	Albumin	Age	BMI
Blood/air partition coefficient of BD	1.00					
Triglycerides	0.61*	1.00				
Total cholesterol	0.29	0.35**	1.00			
Albumin	-0.08	-0.24	0.05	1.00		
Age	0.49*	0.45*	0.18	-0.29	1.00	
BMI	0.30	0.52*	0.44*	-0.34	0.23	1.00

* p \leq 0.05; ** p \leq 0.10.

Table 3. Regression models for the blood/air partition coefficient of BD (n = 24 subjects).

	Cross-sectional model fasting baseline		Longitudinal model without time factor		Longitudinal model with time factor	
	β (SE)	p -Value	β (SE)	p -Value	β (SE)	p -Value
Intercept	1.283 (0.115)	< 0.001	1.239 (0.081)	< 0.001	1.242 (0.081)	< 0.001
Baseline triglycerides (mmol/L)	0.094 (0.028)	0.003	0.109 (0.018)	< 0.001	0.098 (0.017)	0.001
Baseline total cholesterol (mmol/L)	0.030 (0.023)	0.20	0.033 (0.010)	0.004	0.037 (0.011)	0.002
Change in triglycerides (mmol/L)	—	—	0.145 (0.011)	< 0.001	0.086 (0.011)	< 0.001
Time after drinking milk shake (hr) ^a	—	—	—	—	0.042 (0.008)	< 0.001

^aThe blood/air partition coefficient of BD increased approximately linearly over time (χ^2 = 3.0, 1 df, p = 0.08, REML likelihood ratio test, compared to discrete time model).

increase above the baseline of 1.57 ± 0.14 . The pooled coefficient of variation for duplicated measurements of the blood/air partition coefficient of BD was 9%. Of three blood components monitored, only triglycerides showed significant changes in the 4 hr after drinking the milk shake, an average of 123% increase above the baseline. Total cholesterol and albumin levels did not significantly change over time.

Cross-sectional analyses. We used the Spearman correlation matrix to examine the cross-sectional associations of blood and demographic characteristics with the baseline blood/air partition coefficient of BD (Table 2). The blood/air partition coefficient of BD shows significant associations with triglyceride levels ($r = 0.61$, $p = 0.001$) and age ($r = 0.49$, $p = 0.02$). Triglyceride level was also positively associated with age ($r = 0.45$, $p = 0.03$), BMI ($r = 0.52$, $p = 0.01$), and marginally with total cholesterol ($r = 0.35$, $p = 0.10$). The associations of the blood/air partition coefficient of BD with sex, alcohol consumption, or smoking were not statistically significant (data not shown).

We conducted cross-sectional multiple regression analyses for the blood/air partition coefficient of BD as a function of blood triglycerides, total cholesterol, and albumin using a stepwise procedure. Triglyceride level was the only significant predictor variable ($p = 0.003$) (Table 3), and there was no significant quadratic effect of triglycerides on the blood/air partition coefficient of BD (Figure 1).

We also used multiple regression analyses to assess the effects of other explanatory variables or interactions. Although age was significantly associated with the blood/air partition coefficient of BD (Table 2), neither age ($p = 0.51$) nor triglyceride level ($p = 0.19$) was statistically significant when both variables were included in the cross-sectional model. In addition, in this case the regression coefficient for triglycerides decreased from 0.094 to 0.066 (data not shown). Due to the correlation between age and triglycerides, it

was not possible to distinguish the independent contribution of each to the blood/air partition coefficient of BD in a multiple regression analysis. However, we left triglyceride level rather than age in the cross-sectional model because triglyceride level was more significant than age in predicting the blood/air partition coefficient of BD, and age effects intuitively result from triglycerides. In addition, there were no significant interactions between triglycerides and other covariates, and the association of triglycerides with the blood/air partition coefficient of BD did not change appreciably when either sex, smoking, or alcohol consumption was added separately into the cross-sectional model (data not shown).

Longitudinal analyses. As expected from the experimental design, triglycerides increased for all subjects during the first 2 hr following ingestion of the milk shake, and they further increased for 79% ($n = 19$) of the subjects during the second 2 hr, as shown in Figure 2. Most subjects showed a modest increase in triglycerides over the course of the experiment, but two subjects with high baseline triglycerides showed much larger increases with time.

Based on the results of cross-sectional analyses, the longitudinal analyses were focused on the relationship of blood/air partition coefficient of BD to baseline blood constituents and the change in triglycerides over time. In the first longitudinal model without a time factor (as shown in Table 3), both baseline and change in triglycerides were important in estimating the blood/air partition coefficients of BD, although their slopes (0.109 for baseline triglycerides vs. 0.145 for change in triglycerides) were not significantly different from each other ($p = 0.12$). In addition, the precision in estimating the baseline triglycerides effect increased due to a large reduction in the standard error

(SE): the cross-sectional model SE was 0.028 and the longitudinal model SE was 0.018. This might also explain in part why the baseline total cholesterol was statistically significant in the longitudinal analysis but not in the cross-sectional analysis. In the cross-sectional model including both baseline triglycerides and total cholesterol, the slope \pm SE for baseline total cholesterol was 0.030 ± 0.023 ($p = 0.20$) and it had a similar value, 0.033 ± 0.011 ($p = 0.004$), in the longitudinal model.

During the 4-hr study period, the blood/air partition coefficient of BD changed approximately linearly over time ($\chi^2 = 3.0$, 1 *df*; $p = 0.08$, likelihood ratio test, as compared to the discrete time model with measurements taken at three time points). The time after taking milk shake (hours) was also significantly associated with an increased blood/air partition coefficient of BD with a slope of 0.042 ($p < 0.001$), as determined by adding time as a continuous covariate in the longitudinal model (Table 3). The time effect may represent that unmeasured factors related to time also affect the blood/air partition coefficient of BD. Addition of the time factor, however, significantly lowered the regression coefficient for change in triglycerides, from 0.145 ($p < 0.001$) to 0.086 ($p < 0.001$). There is concern about collinearity because change in triglycerides is a function of time after drinking the milk shake, and it is likely that unmeasured time-related factors might also relate to triglycerides. Nevertheless, both the changes in triglyceride level and time were significant in predicting the blood/air partition coefficient of BD; therefore, both were retained in the final (second) longitudinal model. Similar to the cross-sectional analyses, except for age, the results did not alter appreciably with the addition of sex, smoking, or alcohol consumption separately into the final longitudinal model. Adding age into the model reduced the slope and significance for baseline triglycerides from 0.098 ($p < 0.001$) to 0.069 ($p = 0.13$), but it did not substantially affect the parameter estimates for the other explanatory variables. Due to the collinearity between age and triglycerides as shown in cross-sectional analyses, age was not included in the final longitudinal model.

Discussion

In this study we demonstrated that the blood/air partition coefficient of BD was significantly related to triglycerides at baseline and longitudinally associated with baseline triglycerides, total cholesterol, and change in triglycerides over time. The blood/air partition coefficient of BD increased from the average baseline of 1.57 to 1.88 over 4 hr, an average increase of approximately 20%. To our knowledge, this study is the first to

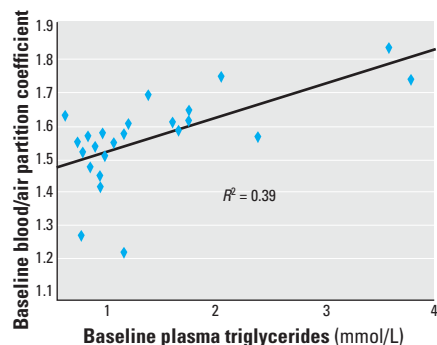


Figure 1. Cross-sectional relationship between baseline blood/air partition coefficient and plasma triglycerides ($n = 24$ subjects).

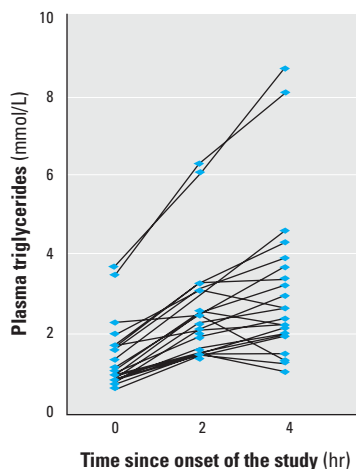


Figure 2. Time course of plasma triglycerides ($n = 24$ subjects). Each line represents one subject.

investigate the changes in the blood/air partition coefficient of BD over time in response to a high-fat meal. The measurements of the blood/air partition coefficient of BD in our longitudinal study were comparable to the values of 1.5 and 1.3 reported by Csanády et al. (20) and Chang et al. (21), respectively, in their cross-sectional investigations.

As shown in our study, BD, a lipid soluble hydrocarbon, is likely to be absorbed and transported in the blood by its blood lipid components, triglycerides and total cholesterol. This relationship is important because many workers exposed to BD may have high lipid diets, and some probably eat high fat meals before they are exposed to BD. Because the blood/air partition coefficient of BD is a major determinant for uptake of inhaled BD (10), high lipid meals may significantly increase their absorbed dose. There were two individuals with high baseline triglycerides who had substantially higher triglycerides after the milk shake than the other subjects, and their blood/air partition coefficient showed a much larger increase, by > 40%. This finding was consistent with previous studies which showed that persons with high fasting triglycerides have a greater increase in triglycerides after a dietary fat load (22–24). This is not due to increased absorption of the fat, but is caused by a reduced clearance rate of chylomicrons and very low density lipoprotein (VLDL) by the liver in these persons. Also, the liver is stimulated to produce VLDL after a meal of fat and sugar (like a milk shake), and some people with high triglycerides have enhanced hepatic production of VLDL. Thus, the absorption of BD and other lipid soluble gases and vapors may be substantially increased in those with high triglycerides.

We also found that the blood/air partition coefficient of BD increased linearly over time after the milk shake, beyond the contribution from the lipids. This may represent an effect of changes in other unmeasured blood constituents after ingestion of the milk shake or simply an underlying diurnal cycle. Previous studies reported that it is possible that multiple blood constituents including cholesterol, triglycerides, and globulin were responsible for blood/air partition coefficient of volatile lipophilic anesthetics such as isoflurane (25). This may pertain to BD as well. Alternatively, the surface area of lipids, chylomicrons, and VLDL change over time postprandially after ingesting a large amount of fat (26) and thereby could affect the blood/air partition coefficient of BD. A specific measurement of chylomicrons and a large VLDL might explain the time effect.

In this study, we found that age relates to both blood/air partition coefficient of BD and triglycerides. Age effects on the blood/air

partition coefficients of some lipophilic chemicals were also found in previous studies. For example, the blood/air partition coefficients of highly soluble inhaled anesthetics, including halothane and methoxyflurane, were significantly higher in adults than in children (27). These demographic effects were assumed to result indirectly from differences in the blood constituents. More recent studies reported that blood lipids, including triglycerides and total cholesterol, vary with age: older people usually have higher levels of blood lipids than younger people (28,29). Due to the limited sample size (24 subjects), the demographic effects in the blood/air partition coefficient of BD might not be clearly defined in this study. Thus, further investigation is needed on the effects of demographic characteristics on the blood/air partition coefficient. In addition, it has been indicated that the solubility of chemical in blood or tissues might depend on the nature of chemicals such as lipophilicity, molecular weight, or surface area (30,31). Therefore, we also recommend research focused on physicochemical structure and dynamics, such as enthalpy or entropy, regarding the partitioning mechanism.

The results and study approaches of this research are directly relevant to other lipophilic gases and vapors of volatile industrial chemicals. It is critical to characterize variations in blood/air partition coefficients of lipophilic chemicals across individuals and across time within the same individual. The blood/air partition coefficient is one of the most important factors that determine respiratory uptake kinetics of gases or vapors; its variability, if significantly sufficiently large, might prevent us from detecting a real exposure–risk relationship because of the misclassification introduced in the internal dose for individuals with similar exposures.

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